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This Month in the *Journal*

Trinucleotide-repeat (TNR) expansions cause diverse human disorders, by several different molecular mechanisms. These mechanisms—or at least the questions that surround them—have begun to come into focus, as shown by the reviews in this issue. Paulson (p. 339) discusses the so-called polyQ diseases, the largest class of TNR disorders, in which long tracts of polyglutamine are expressed in disease-associated proteins. He relates the ongoing controversies about the pathological role of polyglutamine-containing nuclear inclusions in brains of people with Huntington disease or with various spinocerebellar ataxias, and he considers the potential role of protein chaperones in these diseases. Sinden (p. 346) shows how the various disease-associated classes of TNRs affect DNA structure, and he addresses possible mechanisms to account for repeat tract instability at meiosis. Sutherland and Richards (p. 354) discuss chromosome fragility: the best-known fragile sites are TNR expansions that can lead to X-linked retardation, but fragile sites are also common on autosomes, and not all of them contain simple sequence repeats. A TNR expansion in the *DM* gene is also known to cause myotonic dystrophy, a curious finding because the repeat occurs in an expressed but untranslated portion of the gene. Timchenko (p. 360) argues that this expansion interferes with protein-mRNA interactions that are required for normal muscle-cell function. Finally, Knight et al. (p. 365) discuss Friedreich ataxia, an unusual condition associated with an intronic TNR expansion. The discovery of a yeast model for the disease has revealed a previously unsuspected defect in cellular (particularly mitochondrial) iron transport.

Angelman Syndrome in Two Large Families, *by Ohta et al. (p. 385)*

Two papers by Ohta and colleagues focus on the regulation of transcriptional silencing at the two well-studied imprinted loci on 15q that are associated with Angelman syndrome (AS) and Prader-Willi syndrome (PWS). AS occurs when the putative ubiquitin ligase gene *UBE3A*, which is normally expressed only from the maternal chromosome, fails to be expressed at all. Null mutations on the maternal *UBE3A* allele can account for some such cases, but in other AS individuals the defect is in the regulation of the imprinted status. An AS imprinting center (IC) had been defined that is required for the silenced grandpaternal allele to be reactivated as it passes through the maternal germ line. As the authors had reported previously, this "paternal to maternal switch" does not occur on chromosomes with short deletions around the *SNRPN* locus. Now, they report two AS IC deletions that have allowed them to refine the critical interval to a 1.15-kb region ~30 kb from *SNRPN*.

Imprinting Mutations in Prader-Willi Syndrome, *by Ohta et al. (p. 397)*

The effects of IC defects in PWS are analogous to those in AS, although the parental origins are inverted. Hence, passage through the paternal germ line normally reactivates the silenced grandmaternal genes on 15q; deletions in a critical control region prevent the reactivation of the expression of one or more clinically relevant genes. This epigenetic effect is seen when the chromosome that lacks the PWS IC derives from the paternal grandmother. Ohta et al. have mapped several such deletions, and they now show that a necessary part of the regulatory locus occurs in a 4.3-kb region surrounding the promoter and first exon of *SNRPN*. The authors also describe three sporadic instances of PWS IC defects in which no such deletion or other mutation could be found. They speculate that random failure in the reactivation of the grandmaternal allele may lead to some cases of PWS, independent of any DNA sequence changes.

Tau Mutations in FTD Patients, *by Rizzu et al. (p. 414)*

The tau proteins are a set of closely related microtubule-associated proteins that promote tubulin assembly in vitro and that stabilize cellular microtubule arrays in vivo. These proteins, the products of an alternatively spliced RNA from a single locus, have been associated with the progression of Alzheimer disease (AD), because they form fibrils in the amyloid plaques in degenerating AD brain tissues. *TAU* is also implicated more directly in another hereditary neurodegeneration syndrome, frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Rizzu and coworkers have screened for *TAU* mutations in 90 people with frontotemporal dementia. Among 30 independent familial cases, Rizzu et al. report five likely disease alleles, of which two are novel. By expressing wild-type and mutant forms of tau in bacteria, these authors show that purified mutant tau fails to promote microtubule nucleation or growth. The dominant inheritance of FTDP-17 may be explained if these variants have a similar effect in the axon. The unassembled tau proteins may be par-

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ticularly prone to formation of fibrils during or after neuronal death.

Alu *Insertion in* FGFR2 *in Apert Syndrome,* *by Oldridge et al.* (*p. 446*)

The *FGFR2* gene is complex with regard to both its expression and the clinical effects of different mutations. The FGFR2 mRNA is alternatively spliced to encode either the keratinocyte growth-factor receptor (KGFR), normally expressed in epithelial cells, or BEK, a receptor tyrosine kinase found in mesenchymal cells. Mutations that affect one or both of these gene products lead to five distinct human dysmorphology syndromes that affect the skull and other bones, such as the digits. One of these, Apert syndrome, has been associated in every case with point mutations mapping to an extremely short (two amino acids long) region of the FGFR2 proteins. Now, Oldridge et al. have found two counterexamples to this rule. Both of the new alleles result from *Alu*-element insertions located somewhat 3′ to the critical dipeptide region. The finding that one of these mutations leads to the inappropriate expression of KGFR in fibroblasts led Oldridge and coworkers to examine the expression of Kgfr and Bek in the developing mouse limb. On the basis of this analysis, they present a model to explain the effect of ectopic KGFR expression on the separation of digits.

Identification of a Severe Mutation in hGALE, *by Wohlers et al.* (*p. 462*)

Interconversion of charged sugar molecules is required for cellular biosynthesis of complex glycolipids and glycoproteins. The UDP-galactose-4-epimerase (GALE) protein catalyzes one such interconversion, the epimerization of galactose to glucose within the UDP-galactose (UDP-Gal) or UDP-N-acetylglucosamine (UDP-GalNAc) molecules. Missense mutations in *GALE* are known to cause a mild "peripheral" form of galactosemia, in which blood cells lack, but other tissues retain, measurable enzymatic activity. Wohlers and colleagues now show that, in two unrelated families, children with the severe "generalized" form of the disease are homozygous for a novel *GALE* missense allele. Studies of this and other alleles expressed in yeast indicate that the sequence changes lead to loss of activity and/or unstable folding of GALE. However, the clinical phenotype does not always correlate with the activity seen in yeast. The authors also show that GALE mutations can affect activity differently, depending on whether UDP-Gal or UDP-GalNAc is used as a substrate, although only the former substrate usually is tested in galactosemic families.

DNA Variation and Mutation of X Chromosome, *by Anagnostopoulos et al.* (*p. 508*)

Here, Anagnostopoulos and coworkers explore the use of a DNA-mismatch detection system in the study of human variation. The method compares fluorescence-labeled PCR products amplified from one genome with an unlabeled reference sequence to which it is hybridized. Sequence divergences—including nucleotide changes, insertions, or deletions—allow the labeled products to be cleaved chemically, so that the size of the cleaved products can be used to pinpoint the original mismatch, without sequencing. Assuming only that the locations of these PCR products are well mapped on the chromosome, such data are readily used to derive haplotypes. Anagnostopoulos et al. have now applied this approach to a 5-Mb stretch of the X chromosome in 23 men from three distinct ethnic groups, and they also have compared their reference sequence with X-linked DNA from a male chimpanzee. They report the relative frequency of different classes of sequence changes that have occurred during speciation and human migration. This approach also can be adapted to generate long and detailed haplotypes that may be useful in following the evolution of autosomal genes.

Biallelic and Microsatellite Markers in Mapping, *by Xiong and Jin* (*p. 629*)

Xiong and Jin consider the use of likelihood-based disequilibrium mapping and transmission-disequilibrium mapping, in genomewide screens for disease genes. They apply these methods to two classes of polymorphic marker data: multiallelic microsatellite-repeat polymorphisms and biallelic single-nucleotide polymorphisms (SNPs). With both classes of data, they found that the power and precision of the screens are strongly affected by the age of the disease allele and by the population frequency of marker alleles linked to it. The authors indicate that microsatellite markers often will be more powerful, because some rarer alleles may be found at such loci, but a sufficiently dense array of SNPs could overcome this advantage. SNPs are also less susceptible to mutation than are microsatellites; therefore, SNPs may be more suited to fine-structure mapping, in which the rate of recombination between markers may be comparable to the rate at which microsatellite lengths mutate.

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